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Title: Diagnostic practices for patients with shortness of breath and presumed obstructive airways diseases: a cross-sectional analysis	
Authors: Ross T. Tsuyuki, BSc(Pharm), PharmD MSc, William Midodzi PhD, Cristina Villa-Roel MD PhD, Darcy Marciniuk, MD, Irvin Mayers MD, Dilini Vethanayagam MD, Michael Chan MD, Brian H. Rowe MD MSc	
Reviewer 1	Matthew Stanbrook MD PhD
Institution	Toronto Western Hospital, Asthma & Airway Centre, Toronto, Ont.
Reviewer 1 comments	**Authors' Response**
1. Please provide further details regarding participant recruitment: (a) During what time period did participant recruitment take place? Please provide the start and end dates. (b) How were the 28 pharmacies identified or selected as sites for study recruitment? (c) How were patients identified as potentially eligible for the study contacted for enrolment? Did the pharmacists do this themselves, or was the contact information of patients forward to an external study coordinated who then contacted them? (d) Were all participants adults (i.e. were children excluded)? Any other age limits for study inclusion? (e) Any other exclusion criteria not mentioned in the paper? For example, did participants have to speak English? (f) What proportion of participants identified as eligible were ultimately screened and consented?	Thanks for these comments. More details on patients' recruitment have been added to the methods section. a, b, d) Changes made (paragraph 1, page 5): *We used a cross-sectional design, recruiting consecutive patients* ***18 years and older*** *from community pharmacies* ***between February 2009 and 2012****. Twenty-eight pharmacies in Edmonton and Saskatoon, Canada volunteered to enroll patients using the study protocol. There were no inclusion/exclusion criteria for the selection of pharmacists* ***(other than their interest in participating).*** c) Changes made (paragraph 2, pages 5-6): ***Study procedures*** ***Patients meeting the study inclusion criteria were approached by the pharmacist (in-person or over the phone and using standardized scripts) to obtain verbal consent for the project office to make contact by phone. During a telephone call, trained research personnel from the the Epidemiology Coordinating and Research (EPICORE) Centre based at the University of Alberta (www.epicore.ualberta.ca), fully informed patients about the study procedures and asked for their consent to participate.*** e) Thank you, yes, we have now put in the other exclusion criteria. Changes made (paragraph 1, page 5): ***All included patients provided written informed consent; patients*** *were excluded if they were prescribed inhaled medications for symptoms other than SOB (e.g., for a cough only).* ***Patients were also excluded if they could not communicate in English (unless someone could faciliate translation and interpretation), were pregnant, or if they were unable to attend the appointment for pulmonary funtion testing and physical examination.*** f) As per Figure 1, our screening database logged 475 patients, or which 328 were included. But those 475 were

	eligible patients. We do not know how many patients had to be screened to get 475 (we had asked investigators to do that, but we believe they misunderstood and only included those who were eligible).
2. Methods, page 6, 1st paragraph, "Methacholine challenge…was performed in all asymptomatic patients…": (a) Clarify what you mean by "asymptomatic" here. Didn't all patients need to have dyspnea to be enrolled? (b) Regardless, why would you offer methacholine challenge only to asymptomatic patients, rather than to all patients with normal spirometry regardless of current symptoms? Asthma is characterized by a variable symptom pattern.	a) Patients were enrolled on the study based on their current prescription for an inhaled medication for SOB symptoms. Those who did not show evidence of OADs in the initial pre- and post-bronchodilator spirometry underwent methacholine challenge testing. b) Our mistake, we did a methacholine challenge on *all patients with normal spirometry*. We have revised the text to remove the word "asymptomatic". Change made (paragraph 2, page 6): ***Methacholine challenge testing,[20] using the tidal breathing method, was performed in all patients who did not show evidence of OADs in the initial pre- and post-bronchodilator spirometry.***
3. Methods, page 6, paragraph 1: Were any additional PFTs performed other than pre- and post-bronchodilator spirometry and and methacholine challenge? Were lung volumes measured, given that some participants were ultimately diagnosed with restrictive lung diseases? Was diffusion capacity measured, given that some participants were ultimately diagnosed with pulmonary hypertension? If not, how can you be sure that some of the 22.3% with an indeterminate cause for their dyspnea didn't have restrictive lung disease or pulmonary hypertension?	We measured lung volumes and we excluded pulmonary restriction based upon normal TLC. For pulmonary hypertension, we measured diffusing capacity and in combination with elevated BNP led to a presumptive diagnosis of pulmonary hypertension.
4. You describe having reviewed medical records of participants, but little or no information is reported regarding what was found there. (a) How many participants had results of prior PFTs, chest X-rays or echocardiograms in their medical records? Within these, how many showed diagnostic findings (and which diagnoses)? (b) Did you review bloodwork – in particular, hemoglobin level, since anemia is among the causes of dyspnea? (c) If not all participants had evidence of a given test in their medical records, to what extent were the expert panel's diagnostic outcome assessments vulnerable to diagnostic opportunity bias?	We have added information on this regard in the results and limitations sections. Change made (paragraph 2, page 10): *The diagnostic outcomes from the expert physician panel (PFT-derived diagnoses) are shown in Table 4.* ***Information on previous diagnostic tests (e.g., CXR, echocardiogram, methacholine challenge testing, PFTs) was available on 275 patients (84% of the study population).*** Change made (paragraph 2, page 14): *One of the main strengths of our study is the use of standardized diagnostic approaches following the recommendations from international guidelines by an outcome adjudication panel of experts.* ***We collected robust new information and previous diagnostic tests were available for all but 16% of the study population.*** a) We reviewed all available PFTS, CXRs and Echocardiograms but took a fresh, systematic look at each patient. Prior results would guide but would not

	influence our adjudication. b) We did not review bloodwork. We have added an acknowledgment of this in the methods section. Change made (paragraph 2, page 6): *Further, a blood sample for brain natriuretic peptide (BNP) measurement was collected in all patients to rule out heart failure or other heart conditions as underlying entities of the SOB.* ***Complete blood work was not examined.*** c) Thanks for this comment. We have added information on this regard in the limitations section. Change made (paragraph 2, page 14): ***3) the accuracy of our estimates could be affected by the completeness of the information available for assessment. While we did not explore in detail potential sources for diagnostic opportunity bias, we acknowledge that variation in the quality of medical reporting could be an important source for non-differential bias in our study.***
5. Although you defined criteria for classifying participants as having definite or probable asthma or COPD, you appear not to mention definite or probable diagnoses anywhere in the Results section or tables. What proportion of those diagnosed as asthma or COPD were definite v. probable?	Detailed information on definite vs. probable diagnoses for asthma and COPD has been added to Table 4.
6. Results, Diagnostic outcomes, page 9: You provide the rates of diagnostic confirmation, but please provide more information about the rates of misdiagnoses. This is particularly important as you refer to such data in the Discussion section and therefore this needs to be presented first in Results. (a) What proportion of patients previously diagnosed with asthma were not confirmed to have either definite or probable asthma? (b) What proportion of patients previously diagnosed with COPD were not confirmed to have either definite or probable COPD? (c) What proportion of patients previously diagnosed with asthma instead confirmed to have COPD or vice versa? (d) What proportion of patients with other diagnoses were previously diagnosed with asthma or COPD? (e) What proportion of patients with indeterminate causes for dyspnea were previously diagnosed with asthma or COPD?	Details on the proportion of patients with elusive confirmatory diagnosis have been added to the text. Table 5 (added in our first round of revisions) provides more details on the prior PCP diagnoses vs. PFT-derived diagnoses. Changes made (paragraph 2, page 10): • *Of those patients diagnosed with asthma or COPD by our expert physician panel, 11 had both conditions (asthma/COPD overlap* ***syndrome****).* ***Confirmatory diagnosis was elusive in 62 patients (19% of the study sample).*** • *Table 5 revised as described above.*
7. Table 1:	a) We used the standard of 16 mg/mL as the cut-off.

(a) What PC20 cutoff did you use to define airway hyperresponsiveness? (b) For definite COPD, why did you require a post-bronchodilator FEV1 <80% predicted? This would exclude COPD patients with mild (GOLD 1) obstruction. Did you end up classifying any such patients as not having COPD in the end? How could one judge that prescribing inhaled medications to dyspneic patients with mild obstruction is inappropriate?	b) At the time we believed that the majority of GOLD 1 COPD patients would be relatively asymptomatic (de Oca MM, et al., Chest.136:71-8, 2009) and therefore elected to exclude them. In retrospect we should have counted them as COPD even if the likelihood of requiring regular inhaler therapy was low. Based upon this, we reviewed the records of all subjects with FEV1/FVC <0.7 meeting criteria to be considered as possible COPD. A total of 8 subjects eventually met these criteria. Of these 5 of 8 had FEV1 > 95% predicted normal and we believe these are unlikely to represent symptomatic COPD. Only 3 were potentially symptomatic GOLD 1. A sentence to that effect has been added to the results. Change made (paragraph 2, page 10): ***An additional 8 subjects could have been classified as GOLD stage 1 COPD but we elected to include them in the group of indeterminate subjects. The majority of these subjects (5/8) had FEV1>95% predicted normal and, after review, believed that they did not have clinically significant airflow obstruction***
8. Introduction, page 3, "asthma and chronic obstructive airways diseases (COPD)…": Be precise with terminology here. Chronic obstructive airways diseases are a category of several lung diseases that feature obstructive physiology. Chronic obstructive pulmonary disease (COPD) is one specific disease within this category; asthma is another.	Thanks for this comment; we have made this correction**.** Change made (paragraph 1, page 3): *Asthma and* ***chronic obstructive airway disease*** *(COPD) are two of the three most likely diagnoses for obstructive airway diseases (OADs) in a patient with symptoms of shortness of breath (SOB).*
9. Methods, page 5, 2nd paragraph: Please provide more information about these disease-specific symptom measures, as non-specialist readers may be less familiar with some of them. (a) Please mention that the CAT, ACQ, MRC and NYHA are all validated disease-specific symptom measures and provide a suitable reference for each that describes their validation. (b) For the MRC and NYHA scales, please describe what each level of the scale represents (if space is limited, this could be done as an appendix) (c) For the CAT and ACQ, please describe the range of possible values, identify whether higher or lower scores indicate a greater degree of symptoms, provide the minimal clinically important difference and mention the threshold values of each that are	a) This section has been edited. We also added the references that support their validation. Change made (paragraph 1, page 6): *At the testing session, a research coordinator serving as the lead researcher trainee (or designated laboratory technician) collected standardized patient information on socio-demographics, clinical history, and* ***appropriate validated disease-specific measures through self-report of the*** *COPD assessment test (CAT;* ***eight-item questionaire that provides a 0-40 score from less to more severe impact of COPD on a patient's life), the*** *Asthma Control Questionnaire (ACQ****; 7-point scale that provides a 0-6 score from no impairment to maximum impairment for symptoms and rescue use in patients with asthma****), the functional capacity using the Medical Research Council (MRC) dyspnea scale* ***(five-item scale that provides a 1-5 score from none to almost complete incapacity to breath in patients with cardio-respiratory conditions)*** *and* ***the*** *New York Heart*

generally considered to distinguish more symptomatic from less symptomatic patients. (d) Were all participants evaluated on all 4 scales? Or were scales administered based on the nature of participants' self-reported diagnoses? The Results section suggests the latter.	*Association* ***(NYHA)*** *Functional Classification Scale (****four-item scale that provides a 1-4 score from no to severe limitation in physical activity in patients with heart failure****).*[15-18] b and c) In the first round of revisions we added an appendix with the study forms (including what each level of the MRC, NYHA, CAT and ACQ scales represent). We have edited the methods section to include more information on these scales (see our response to the previous question above). The range of scales has been included, as described above. We did not provide information on the MCIDs because this was not an intervention trial. d) Scales were administered based upon the nature of patients' self-reported diagnoses. Change made (paragraph 1, page 6): Please see above.
10. Methods, Study outcomes, page 6: Please clarify that it is your definitions of definite asthma or COPD that are based on standardized criteria in the international guidelines. Your criteria for probable asthma or COPD (i.e. opinion of the expert panel) are not, although there is some face validity in this.	Yes- our definitions were based on standardized approaches- at the time we used CTS asthma and COPD guidelines criteria.
11. In the Introduction, you refer to "recent" studies of asthma or COPD under- or overdiagnosis, but among the references you cite here and in the Discussion section, only #9 and # 10 are within the last decade (#8, for example, is from 2003, which isn't really recent). However, there have been several such studies involving Canadian patients that have been published in the last few years that might provide a more up-to-date context for your study: Gershon et al., Chest 2018;153:1336-46 Gershon et al., European Respiratory Journal 2016;48:561-4 Diab et al., American Journal of Respiratory and Critical Care Medicine 2018;198:1130-9.	Thanks for this comment. We have added the suggested references.
12. Results, Patient characteristics etc., page 8, last paragraph: You refer to the mean +/- SD score for both the ACQ and the CAT, but then you provide interquartile ranges. Are these results actually medians and IQRs?	These results are reported as medians and IQRs.
13. Table 2:	a) Further information on ethnicity and education has

(a) Can you provide a further breakdown of participant data on ethnicity and education, rather than just listing how many were white and had post-secondary education? This is important for generalizability. (b) Were any other comorbidities measured beyond the 5 listed? Heart failure, cardiovascular disease, anemia and connective tissue diseases would all seem particularly relevant. (c) Were symptoms, other symptoms, and absenteeism assessed in all patients? Or only in a subset who received the ACQ or CAT? (d) Do you have data on any other parameters of asthma control, i.e. nocturnal awakenings and reliever use?	been provided in Table 2. b) Other relevant co-morbidities have been reported on Table 2. Unfortunately, we didn't assess the presence of connective tissue diseases. c) The symptom that are summarized on Table 2 were assessed on the entire study population. d) Unfortunately, not. Nocturnal cough, which was combined with daytime cough on Table 2, was our proxy to nocturnal awakenings.
14. Table 3: (a) Can you expand this table to provide an additional column for participants who had no previous diagnosis of either asthma or COPD? (b) Did any patients have a previous diagnosis of both asthma and COPD (or asthma-COPD overlap)? If so, please report this in a footnote. (c) Did no patients receive a LABA/LAMA or a LABA alone? The latter would not be that surprising in a fairly small cohort, but the former would be.	a) Further information on participants with no previous diagnosis of either asthma or COPD has been provided in Table 3. b) Yes, a foot note has been added. c) Three patients were on LABA alone (and SABA): one participant with previous diagnosis of asthma and two participants with no previous diagnosis of either asthma or COPD.
15. Table 4: "Bronchitis" is a clinical syndrome, not a diagnosis. Do you mean acute viral bronchitis?	The term bronchitis was used to denote various etiologies (likely viral), but we did not specify as the underlying infectious etiology was not known with certainty.
16. Please avoid acronyms that are not both commonly used and broadly familiar (e.g. OAD, MCC) and those that are potentially confusing (e.g. ECG is widely used to mean an electrocardiogram, not an echocardiogram).	We have decided to leave the acronym OAD. Following your advice, we removed MCC and ECG.
Reviewer 2	Jayaprakash Chinnappan
Institution:	Bioinformatics, Bharathiar University, India
Reviewer 2 comments	Authors' Response
Congratulations for All the Authors for this patients study. It is a newly interested topic. Which has lot of new and acceptable information.	Thanks for this positive comment.
1. Materials and Methods: Page no 6 of 23 Study design, setting and participants. Line 8 and 9 (Patients were.....for follow-up). This sentence will make confusion to the readers. So, you may modify this.	Thanks for this comment. Change made (paragraph 1, page 5): ***Patients were also excluded if they could not communicate in English (unless someone could faciliate translation and interpretation), were pregnant, or if they were unable to attend the***

	appointment for pulmonary funtion testing and physical examination.
2. Study procedures. A word in Line 8 and 9 (PCP). In lung diseases Pneumocystis carini pneumonia also means PCP. So,You may avoid the short word PCP here and use the full form.	Thanks for this comment. We have removed this acronym from the text and tables.
3. Page no 8 of 23 Sample size and data analysis Line 1 (A total of 323). Previously mentioned 328 in two places. So, is this correct or incorrect. Kindly check it.	Thanks for this comment. We have corrected this typo.
4. Conclusions Page 14 of 23 Line 1 (In our study, we found that fewer than half ..... Line 4 less than a half had ever...). Here you may say the exact percentage what you received from the 328 patients. Also conclusions need some clarity.	We have added the exact percentages to this section. Change made (paragraph, page 16): *In our study, we found that fewer than half of community-dwelling patients being treated with inhaled medications for SOB and presumed OADs, had confirmed asthma* ***(45.4%)****, approximately a quarter had COPD* ***(29.6%)****, and a further quarter had no demonstrable OADs* ***(25%)****. This, coupled with the fact that less than a half had ever had PFT performed* ***(40.8%)****, highlights the need to avoid empiric treatment with β-agonists and ICS agents, increase the use of objective measures of lung function for the diagnosis of OADs, and identify factors associated with* ***patient*** *misdiagnosis* ***(e.g., obesity, gastro-esophageal reflux, etc.).***
5. Also correct the dot(.) and commas(,) of the whole paper.	Done, thanks.